

Discontinuation of Lubiprostone Treatment for Irritable Bowel Syndrome With Constipation is Not Associated With Symptom Increase or Recurrence: Results From A Randomized Withdrawal Study

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Background

- Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder with an estimated prevalence of 10–15% in Western countries.
- Diagnosis of IBS is based upon the presence of abdominal discomfort/pain with changes in bowel habits. In clinical practice and research, IBS patients are subgrouped on the basis of differences in bowel habits. Approximately 1/3 of IBS patients suffer with IBS and constipation (IBS-C).
- Current therapies for IBS-C tend to target relieving individual symptoms of constipation, abdominal pain or bloating rather than the totality of IBS symptoms.
- Lubiprostone, a selective activator of type-2 chloride channels (ClC-2), is approved for the treatment of chronic idiopathic constipation in adults and for the treatment of IBS-C in adult women.
- Lubiprostone enhances fluid secretion into the intestinal lumen without altering serum electrolyte levels.
- Patients with IBS may exhibit abnormal gut permeability and an associated intestinal inflammatory response. Lubiprostone stimulates recovery of mucosal barrier function in animal models suggesting a possible mechanism for the clinical improvement observed in patients on this drug.*
- Given the intermittent nature of IBS-C symptoms, short-term interventions for symptomatic relief of IBS-C may be appropriate in some patients. Such interventions need to be efficacious and not associated with rebound effects following discontinuation of treatment.

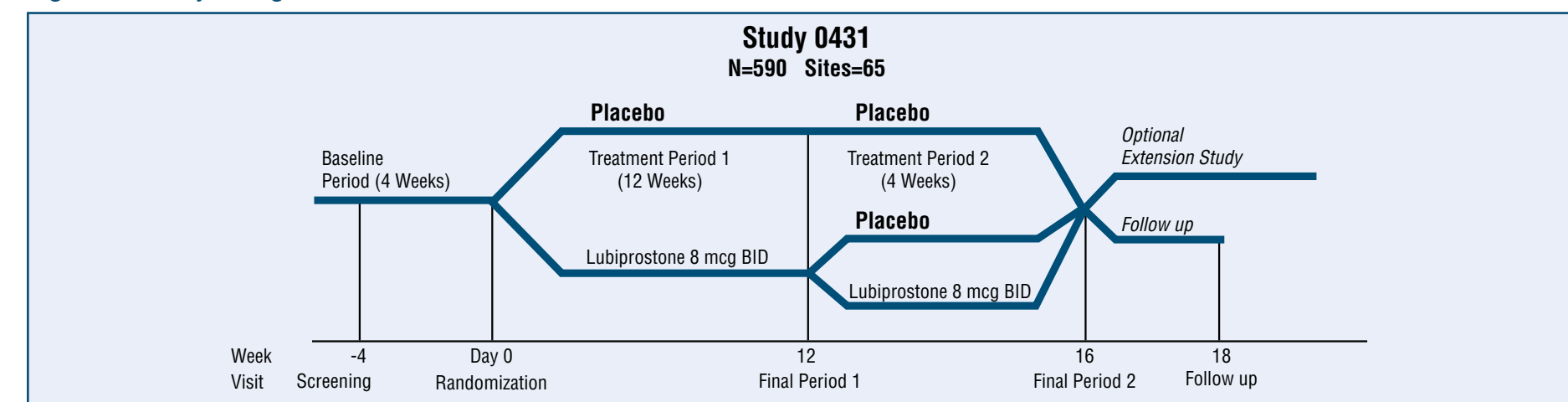
Objective

- To ascertain whether there are any rebound effects upon randomized withdrawal (RW) of lubiprostone after 12 weeks of treatment.

Methods

- This was a randomized, double blind, placebo-controlled, multicenter (65 centers in the US) Phase 3 trial consisting of 2 treatment periods (Figure 1).
 - Treatment Period 1** evaluated the efficacy and safety of lubiprostone for the treatment of IBS-C for 12 weeks.
 - Treatment Period 2** evaluated the lasting or rebound effects of RW of lubiprostone for 4 weeks.
- At the beginning of Treatment Period 1, 590 patients were randomized in a 1:1:1 ratio to receive either 16 mcg lubiprostone (8 mcg BID) during both treatment periods, 16 mcg lubiprostone during Period 1 and placebo BID during Period 2, or placebo BID during both periods. A total of 436 patients completed Treatment Period 1 and entered Treatment Period 2 (Figure 2).
- Efficacy endpoints included the overall responder rate during Treatment Period 1 (Weeks 1-12), responder rate during Treatment Period 2 (Weeks 13-16), and patient evaluation of IBS symptoms.
 - Patients evaluated their IBS-C symptoms (abdominal discomfort/pain, spontaneous bowel movement (SBM) frequency rates, stool consistency, bowel straining, constipation severity, and abdominal bloating) in an electronic diary on a daily basis. Abdominal discomfort, abdominal bloating, and constipation severity were assessed using a 5-point severity scale where 0=Absent, 1=Mild, 2=Moderate, 3=Severe, and 4=Very Severe. The 5-point scale for stool consistency was 0=Very Loose, 1=Loose, 2=Normal, 3=Hard, and 4=Very Hard.
 - Symptom relief was assessed on a weekly basis using a 7-point balanced scale in response to the following question:
 - "How would you rate your relief of IBS symptoms (abdominal discomfort/pain, bowel habits, and other IBS symptoms) over the past week compared to how you felt before you entered the study?"
 - 3 (Significantly worse), -2 (Moderately worse), -1 (A little bit worse), 0 (Unchanged), +1 (A little bit relieved), +2 (Moderately relieved), +3 (Significantly relieved)
 - Monthly responders were defined as those whose symptoms were rated as at least "moderately relieved" for all 4 weeks within a month or "significantly relieved" for at least 2 weeks within a month — provided that the percent of days of rescue medication use did not increase during the month compared to baseline, the patient did not discontinue due to lack of efficacy, and there were no ratings during the month of "moderately worse" or "significantly worse."
 - An overall responder was defined as one who was a monthly responder for at least 2 of the 3 months of Treatment Period 1.
- Rebound effect was defined as symptoms recurring or having a greater rate or intensity at the end of Treatment Period 2 (Week 16) when compared to measurements taken at the end of Treatment Period 1.
- Study populations were defined as follows:
 - All patients who took at least 1 dose of the study medication dispensed at Week 12 comprised the RW Treatment Period 2 Population.
 - The subset of RW patients who were overall responders during Treatment Period 1 comprised the period 1 Responder Population.

Figure 1. Study Design



*Camilleri M, Gorman H. Intestinal permeability and irritable bowel syndrome. *Neurogastroenterol Motil* (2007) 19, 545-552. E001401

Results

- Responder rate during Treatment Period 1 was significantly higher in the lubiprostone-treated patients than among those receiving placebo (13.8% vs. 7.8%, P=0.029; Figure 3).
- At the end of Treatment Period 2, responder rates among the entire RW Population in the lubiprostone/placebo group and the placebo/placebo group were 11% and 7.9%, respectively, indicating that withdrawal of lubiprostone had no rebound effect on responder status (Figure 3).
- At the end of Treatment Period 2, responder rates among the Period 1 Responder Population in the lubiprostone/lubiprostone and the lubiprostone/placebo groups were 38.1% and 40%, respectively, indicating that patients in either group were equally likely to experience sustained symptom improvement (Figure 4).
- At Week 16, IBS-C symptoms of abdominal discomfort/pain, bloating, SBMs, stool consistency, degree of straining, and constipation severity were not significantly different between the lubiprostone/placebo and lubiprostone/lubiprostone groups indicating that withdrawal of lubiprostone had no rebound effect on symptoms (Table 3).

Figure 2. Disposition of Patients

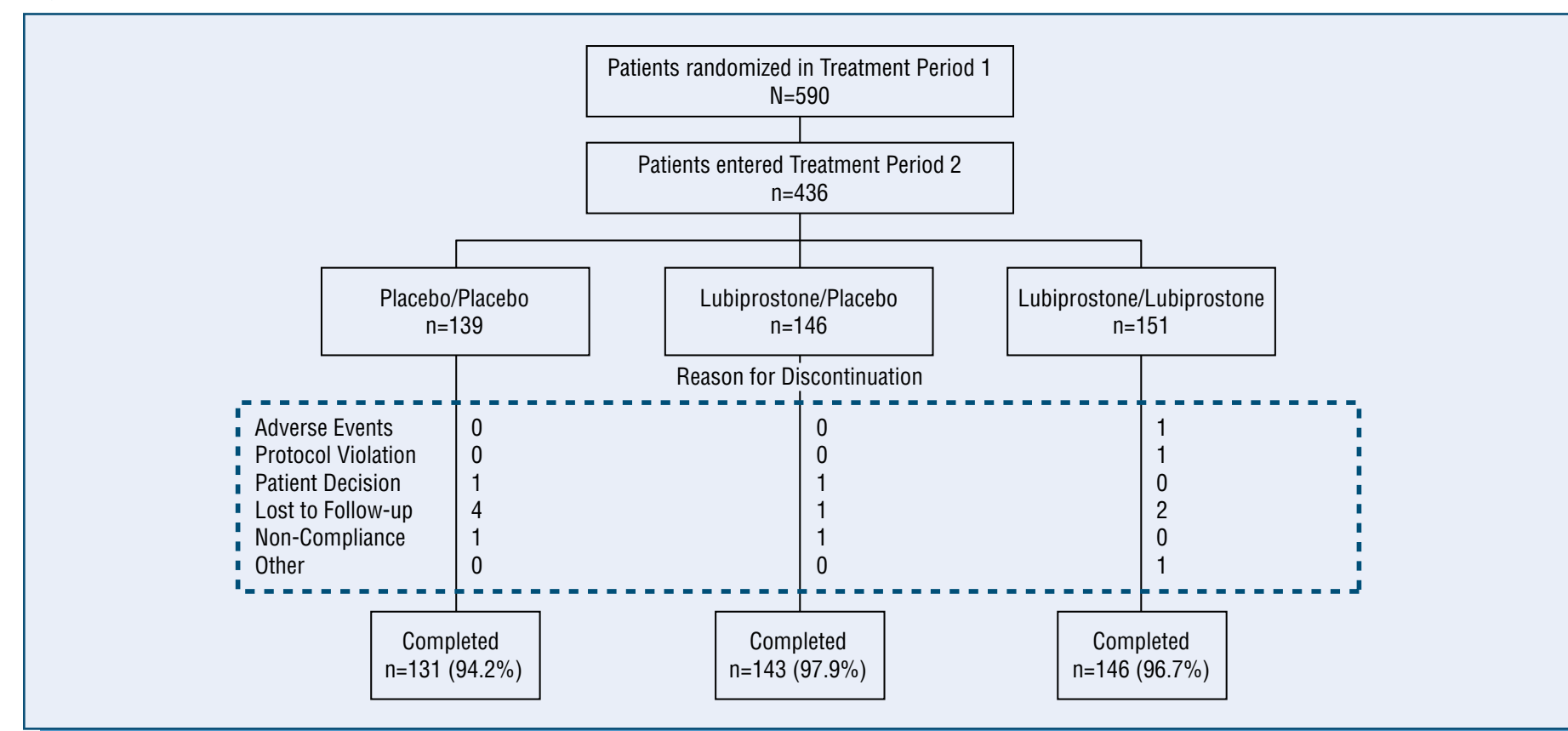


Table 1. Baseline IBS-C Symptoms – Treatment Period 1 (Randomization)

| Variable | Placebo n=193 Mean (SD) | Lubiprostone n=390 Mean (SD) |
|--|----------------------------|---------------------------------|
| Abdominal Discomfort/Pain ¹ | 2.09 (0.7) | 2.08 (0.7) |
| Abdominal Bloating ¹ | 2.28 (0.7) | 2.27 (0.7) |
| Constipation Severity ¹ | 2.29 (0.6) | 2.24 (0.7) |
| Weekly SBM Frequency | 3.69 (3.3) | 3.76 (3.2) |
| SBM Stool Consistency ² | 2.74 (0.6) | 2.78 (0.6) |
| SBM Bowel Straining ¹ | 2.41 (0.7) | 2.38 (0.7) |

¹Scale: 0 (Absent), 1 (Mild), 2 (Moderate), 3 (Severe), 4 (Very Severe)
²Scale: 0 (Very Loose), 1 (Loose), 2 (Normal), 3 (Hard), 4 (Very Hard)

Table 2. Demographic Characteristics of All Patients in RW Population

| Characteristic | Enrollment Group | | |
|------------------------|------------------------------|-----------------------------------|--|
| | Placebo/ Placebo n=139 | Lubiprostone/ Placebo n=146 | Lubiprostone/ Lubiprostone n=151 |
| Age (yrs) | | | |
| Mean (SD) | 47.9 (12.8) | 45.1 (10.9) | 47.9 (13.8) |
| Range | 21–82 | 20–73 | 20–83 |
| Gender (F/M) | 128/11 | 137/9 | 136/15 |
| Race, n (%) | | | |
| Caucasian | 105 (75.5) | 107 (73.3) | 121 (80.1) |
| Black/African American | 19 (13.7) | 21 (14.4) | 13 (8.6) |
| Hispanic/Latino | 11 (7.9) | 18 (12.3) | 17 (11.3) |
| Other | 4 (2.9) | 0 (0.0) | 0 (0.0) |

Figure 3. Overall Responder Rates in Treatment Period 1 (Weeks 1-12) and Monthly Responder Rates of All Patients in RW Population in Treatment Period 2 (Weeks 13-16)

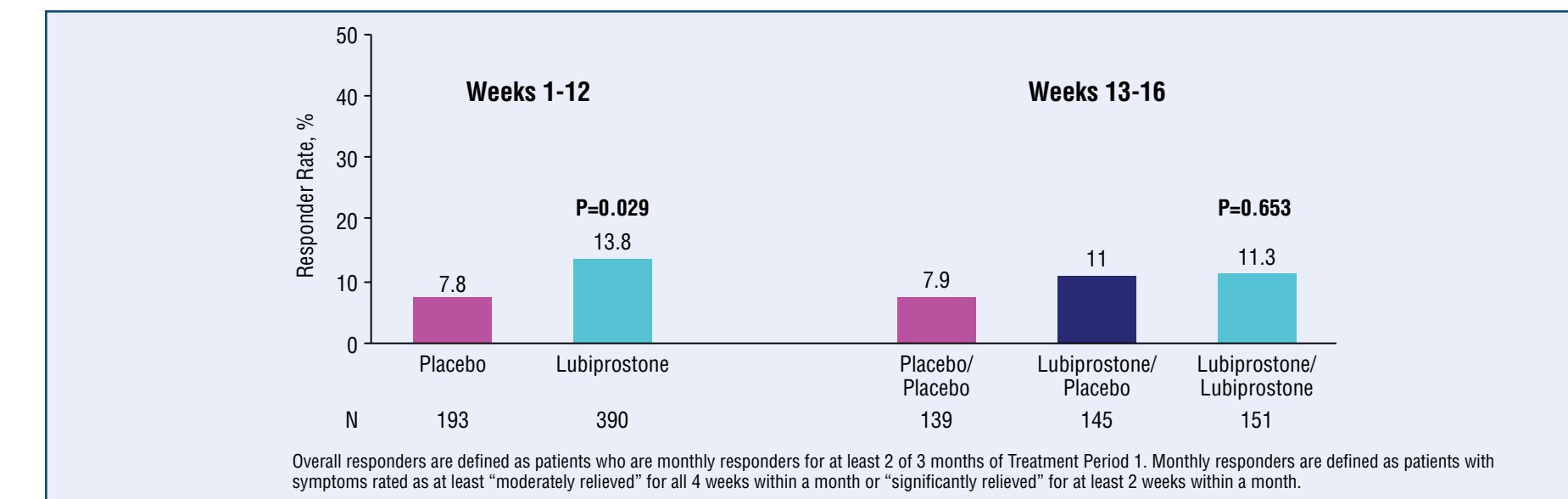


Figure 4. Responder Rates of Period 1 Responder Population in Treatment Period 2 (Weeks 13-16)

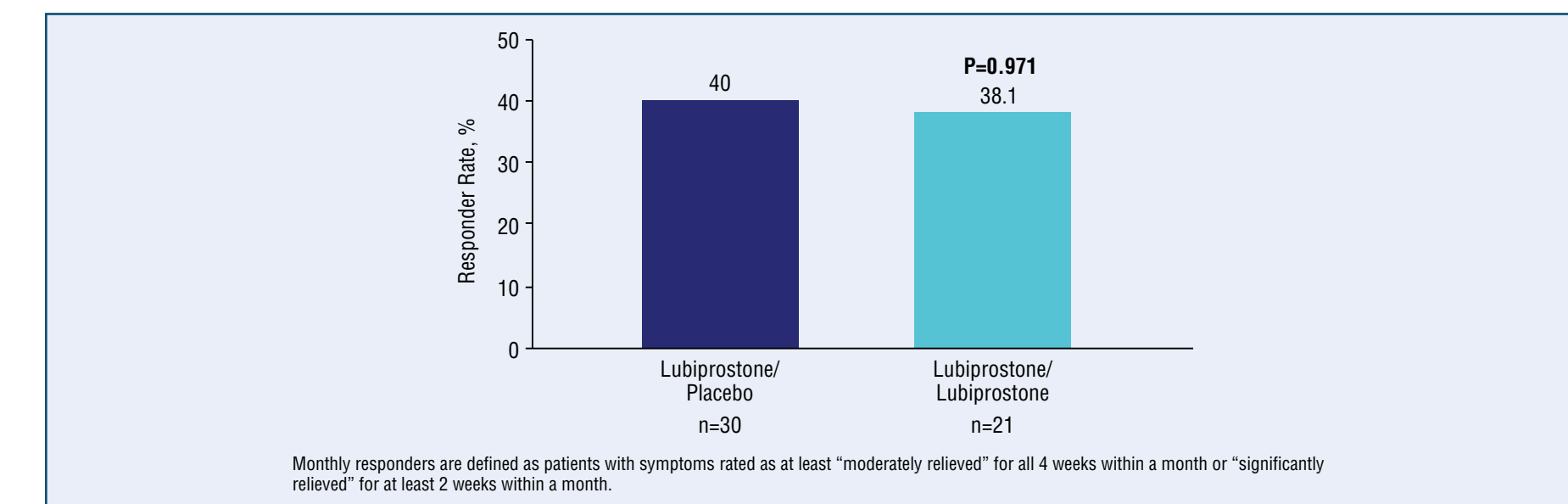


Table 3. IBS-C Symptoms of Patients in RW Population at End of Treatment Period 1 (Week 12) and End of Treatment Period 2 (Week 16)

| Variable | Lubiprostone/Placebo n=145, mean (SD) | | Lubiprostone/Lubiprostone n=151, mean (SD) | |
|--|--|------------|---|------------|
| | Week 12 | Week 16 | Week 12 | Week 16 |
| Abdominal Discomfort/Pain ¹ | 1.56 (0.9) | 1.62 (0.9) | 1.54 (0.8) | 1.60 (0.8) |
| Abdominal Bloating ¹ | 1.77 (0.9) | 1.79 (1.0) | 1.72 (0.9) | 1.75 (0.9) |
| Constipation Severity ¹ | 1.63 (1.0) | 1.67 (1.0) | 1.66 (0.9) | 1.73 (0.9) |
| SBM Frequency Rate ² | 5.97 (5.3) | 6.17 (6.1) | 5.29 (3.4) | 5.47 (3.5) |
| Stool Consistency ³ | 2.22 (0.7) | 2.45 (0.7) | 2.31 (0.8) | 2.24 (0.9) |
| Degree of Straining ¹ | 1.70 (0.9) | 1.87 (0.9) | 1.71 (0.9) | 1.75 (0.9) |
| Symptom Relief ⁴ | 0.94 (1.5) | 0.67 (1.5) | 0.89 (1.3) | 0.82 (1.4) |

¹Scale: 0 (Absent), 1 (Mild), 2 (Moderate), 3 (Severe), 4 (Very Severe); ²SBM frequency rate: (number of SBMs/number of days observed for that week)x7; ³Scale: 0 (Very Loose), 1 (Loose), 2 (Normal), 3 (Hard), 4 (Very Hard); ⁴Scale: -3 (Significantly worse), -2 (Moderately worse), -1 (A little bit worse), 0 (Unchanged), 1 (A little bit relieved), 2 (Moderately relieved), 3 (Significantly relieved)
 *All differences between treatment groups were not statistically significant.

Conclusion

- Lubiprostone is effective in relieving the symptoms of IBS-C and is not associated with symptom rebound for up to 4 weeks following discontinuation of treatment.